AD_____

Award Number: DAMD17-99-1-9498

TITLE: SPECT and fMRI Analysis of Motor and Cognitive Indices of Early Parkinson's Disease: The Relationship of Striatal Dopamine and Cortical Function

PRINCIPAL INVESTIGATOR: John D. Gabrieli, Ph.D.

CONTRACTING ORGANIZATION: Rush-Presbyterian-Saint Luke's Medical Center
Chicago, Illinois 60612

REPORT DATE: October 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Annual (1 Oct 00 - 30 Sep 01)

4. TITLE AND SUBTITLE
SPECT and fMRI Analysis of Motor and Cognitive Indices of Early Parkinson's Disease: The Relationship of Striatal Dopamine and Cortical Function

5. FUNDING NUMBERS
DAMD17-99-1-9498

6. AUTHOR(S)
John D. Gabrieli, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Rush-Presbyterian-Saint Luke's Medical Center
Chicago, Illinois 60612

E-Mail: gabrieli@psych.stanford.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

14. SUBJECT TERMS
Neurotoxin

15. NUMBER OF PAGES
8

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Annual Report
USAMRMC Neurotoxin Exposure Treatment Research Program

Grant #: DAMD17-99-1-9498

Principal Investigators: John D. E. Gabrieli, Ph.D.
Glenn T. Stebbins, Ph.D.

Institution: Rush-Presbyterian-St. Luke's Medical Center

Grant Title: SPECT and fMRI Analysis of Motor and Cognitive Indices of Early Parkinson's Disease: The Relationship of Striatal Dopamine and Cortical Function

Comments to Previous Annual Report Review

Summary Recommendations, Discrepancies, and/or Technical Assistance

The reviewer strongly recommended that issues regarding ligand procurement and approval, and delay-of-funding request be addressed as soon as possible. We have now received HSRRB approval for the project (see text below), as well as FDA approval (IND # 60,953), and approval for an Extension Without Funds.

Request for Additional Information on Analytic Technologies for Combining Different Imaging Types

We have develop a Matlab code for stripping header information from various image modalities and substituting a widely used header format (ANALYZE format). This substitution allows for importation of the images into various analysis programs including SPM99 (our major analytic tool), Analyze from the Mayo Clinic, and IDL based analytic tools.

Progress Report for DAMD17-99-1-9498

The goals for the second funding period of this award were as follows:

2. **Data collection and analysis (12 months)**
- At least 54 participants identified from our cohort of PD, HA, and YNC will be scheduled for testing
- Recruitment and enrollment will continue for the additional participants required
- Analysis of behavioral data collected in this time period will be scored
- Analysis of fMRI data and SPECT data will be analyzed and co-registered
- An abstract will be prepared for the Society for Neuroscience Conference
- Annual progress report requested by sponsor will be completed

Goals 1: Data collection and analysis (12 months)

We have not met all of the goals for #1. We had not been able to test any subjects because of a delay obtaining approval from the Human Subjects Research Review Board of Regulatory Compliance and Quality at the USAMRMC. On December 20, 2001 we were notified by Dr. Adriene King of AMDEX that the HSRRB had approved our project for initiation and had send a memo of approval to Ms. Sacelia Heller, our Contract Specialists at the U.S. Army Medical Research Acquisition Activity. We are now authorized to begin recruitment and testing of subjects and will enroll our first cohort of 50 within the first two quarters of this year.

The process of obtaining approval from the HSRRB was very lengthy, extending from the initial award notice to the present time. We had loss access to the original ligand we proposed to use of SPECT scanning of the dopamine system and had to seek FDA approval for use of a different ligand. This approval was awarded in October of 2000. Following FDA approval, we

1725 West Harrison, Suite 309, Chicago, IL 60612 Tel: (312) 563-3854 Fax: (312) 942-2380 email: gstebbin@rush.edu

had to reapply for approval from our Radiation Safety Committee for a new radioisotope authorization number, approval of the change in protocol from our Institutional Review Board, and approval from the HSRRB. Because of the delay in obtaining approval, we sought a 10 month extension without funds. This extension was granted in early 2001. With the final approval of the HSRRB, we can finally begin the recruitment and testing of participants.

While awaiting approval from the HSRRB, we have completed development of all imaging and behavioral testing protocols, data recording forms, Clinical Report Forms, and Safety Monitoring Forms. In addition, we have developed and tested the analytic techniques for combining different imaging data types, including co-registration of structural, functional, and SPECT images, normalization of brain images to a common atlas, and statistical analyses of the resultant data. These procedures are in place and will be easily implemented when we acquire our data.

Development of a Novel Scanning Paradigm for Assessment of White Matter Integrity

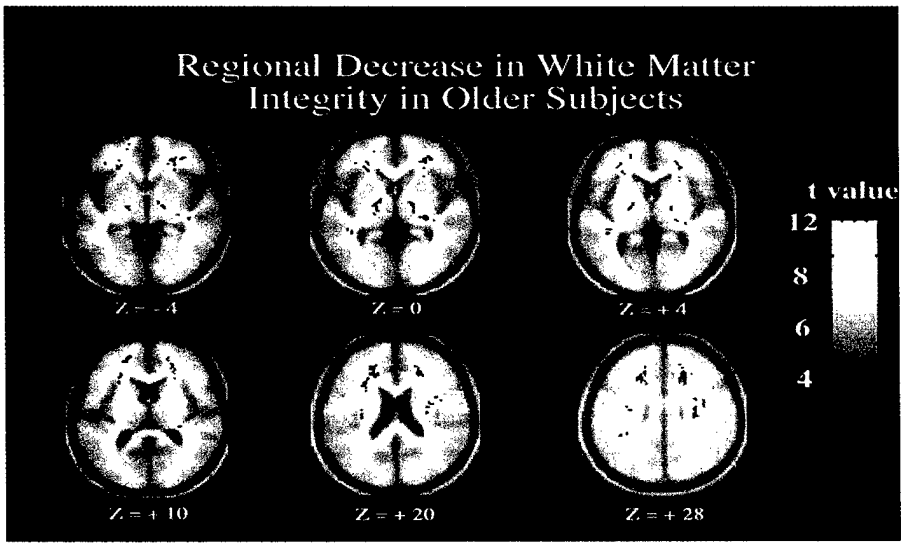
In addition to completing these initial phases of the study, we have developed a new scanning protocol for the examination of the microstructural integrity of white matter. We plan to include this protocol in the study. The acquisition time for the scan is approximately four minutes. There is no increased risk with this scan (it is a standard MRI pulse sequence), and the increased benefit of detailed information on white matter integrity outweighs the inconvenience of an additional four minutes scan time.

The technique we are developing is an advance in diffusion weighted MRI that provides additional information relevant to the structural integrity of the brain in general and the white matter specifically. Diffusion Tensor Imaging (DTI) is an existing MRI scanning paradigm that makes possible the examination of alterations in the microstructure of cerebral tissue *in vivo* and is especially indicative for diseases causing neuronal or axonal damage. The technique is based on sensitizing the MR signal to movement of water on the order of several microns (diffusion weighted MRI) and measuring the direction and magnitude of water diffusion in six non-collinear gradients simultaneously. The application of six non-collinear gradients allows for examination of diffusion characteristics irrespective of head position. The three-dimensional geometry of the diffusion in a particular volume element (voxel) can be described by a mathematical construct called a "tensor" that can be represented by a 3x3 matrix.. From the diffusion tensor in each voxel, one can derive three eigenvectors, defining the magnitude and direction of the diffusion system, with the corresponding eigenvalues λ_1, λ_2 and λ_3. The average of the three eigenvalues represents the mean molecular motion (average diffusivity: DW) which is affected by barriers to diffusion but does not provide information on the directionality of the diffusion. Based on the three eigenvalues, and the mean eigenvalue ($\underline{\lambda}$) the intra-voxel organization of diffusion direction can be measured as the fractional anisotropy (FA), yielding values between 0 and 1, with 0 indicating completely random diffusion (isotropic diffusion) and 1 representing completely directional diffusion (anisotropic diffusion). CSF has extremely low FA values because hydrogen is free to diffuse in any direction. Gray matter has medium FA because cellular structures (e.g., cell membrane, organelles) impede the free diffusion of hydrogen. Highly organized white matter tracts have high FA because hydrogen diffusion is highly constrained by the tract's cellular organization. In addition, the integrity of diffusion direction between voxels can be derived providing a measure of inter-voxel coherence (C). This measure assesses the mean angle of principal diffusion directions between each voxel and its eight neighboring voxels with values ranging from 0 (no coherence) to 1 (unity of direction). We have developed a method of incorporating the DTI scans into SPM format for analysis. Specifically, we have developed a program that transforms the image header information into a format that is readable by most standard image analysis software. In addition, we have applied normalization routines that transform individual brains to a standard template, allowing for comparison between groups of

1725 West Harrison, Suite 309, Chicago, IL 60612 Tel: (312) 563-3854 Fax: (312) 942-2380 email: gstebbin@rush.edu

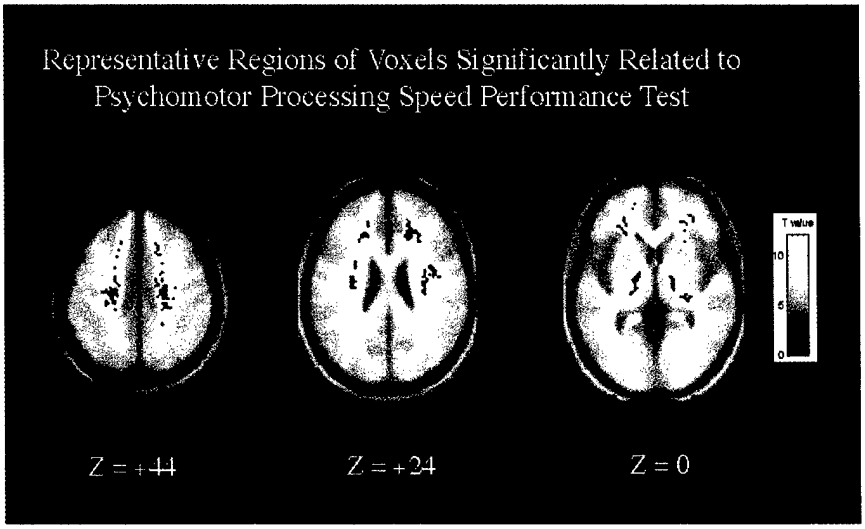
subjects. We will use DTI in the present project to examine the integrity of white matter tracts extending from the substantia nigra (the location of doapmine producing cells in humans) to the striatum and from the striatum to the cortex. We hypothesize that age-associated and Parkinsonian damage to the dopaminergic system will be reflected in decreased white matter integrity in these tracts. This will allow us to develop a more complete understanding of the effects of dopamine depletion on sites of dopamine production (the substantia nigra), transmission (white matter tracts), subcortical utilization (the striatum), and cortical function.

In support of the use of this technique, we have completed a pilot study using a sample of 10 healthy young participants, 10 healthy older participants, and 10 participants with Parkinson's disease. Scans were performed on a 1.5 T GE scanner equipped with fast gradient Horizon Echospeed upgrades (Rev. 8.4). Single-shot echoplanar diffusion-weighted imaging was used. Post processing of DT-MRI images involved the unwarping of eddy currents and the calculation of the six diffusion coefficients defining the six elements of the diffusion tensor. The fractional anisotropy (FA) was derived from the eigenvalues. Individual participant slice images for FA were concatenated into whole-brain volumes in acceptable format using software developed by our consultants. Whole-brain volumes were imported into SPM99 software for analysis. All images were spatially normalized to a standard template and masked to exclude voxels from gray matter, CSF, and to exclude atrophic differences between younger and older brains. Using a voxelwise threshold of $p < .05$, and a spatial extent threshold of $p < .05$ to correct for multiple comparisons at the clusterwise level, group differences in FA between younger and older participants, were assessed using the two sample t-test statistic in SPM. Whole-brain, atrophy-corrected white matter FA was significantly lower in older compared to younger participants (Older M = 0.352 (sd 0.02); Younger M = 0.412 (sd 0.02): $t(18) = 7.60$, $p < .001$). There was virtually no overlap in FA values between the groups. Analysis of regional differences in atrophy-corrected white matter FA revealed significant age-associated reductions in bilateral posterior frontal white matter fields, bilateral cingulate sub-gyral white matter, bilateral precuneus parietal sub-gyral white matter, and bilateral posterior limbs of the internal capsule. Additional age-associated decreases were found in the left anterior frontal white matter fields and the left supramarginal parietal sub-gyral white matter. No regions of significant age-associated increase in anisotropy were detected (see Figure below).



1725 West Harrison, Suite 309, Chicago, IL 60612 Tel: (312) 563-3854 Fax: (312) 942-2380 email: gstebbin@rush.edu

Whole-brain, atrophy-corrected white matter fractional anisotropy was significantly correlated with psychomotor processing speed performance (FA:SDMT r = .779, p < .001). Regressing psychomotor processing speed performance on FA while first removing aging effects revealed significant associations between SDMT scores and white matter integrity in bilateral middle frontal white matter fields and bilateral posterior limbs of the internal capsule (see Figure below).



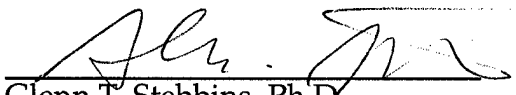
This results suggest regional changes in frontal white matter integrity and white matter integrity of the internal capsule in normal aging. The dopaminergic outflow from the striatum and thalamus courses through the anterior and posterior limbs of the internal capsule to the frontal lobes and diffuse cortical regions. The decrease in microstructural integrity of white matter in these regions, may help explain age-associated changes in dopamine mediated cognition. As white matter integrity decreases, processing speed in effected, which, in turn, affects other executive processes that decline with age. This paper was presented at the 2001 annual meeting of the American Academy of Neurology (Neurology 2001;56 (Suppl 3):A374) and is submitted for publication.

Examination of DTI imaging differences between healthy aging and Parkinson's disease revealed additional regions of decreased white matter integrity. Specifically, PD patients showed decreased white matter integrity within areas that appeared normal on standard MRI examination. Overall anisotropy was significantly decreased in the PD sample compared to the older sample (PD M = .287 (sd 0.02); Older Controls M = .352 (sd 0.02), t(18) = 6.49. p < .001). Regions of significantly decreased anisotropy in the PD sample were primarily found in the frontal white matter fields, the posterior limb of the internal capsule, and corona radiata adjacent to primary motor and sensory cortices. Posterior regions did not evidence significant differences. Decreases in normal appearing white matter integrity significantly correlated with a measure of processing speed (SDMT r = .78, p < .01). These results suggest a further decline in white matter integrity associated with the dopaminergic system in patients with Parkinson's disease. This paper is submitted as an abstract to the 2002 annual meeting of the American Academy of Neurology.

1725 West Harrison, Suite 309, Chicago, IL 60612 Tel: (312) 563-3854 Fax: (312) 942-2380 email: gstebbin@rush.edu

We are anxious to start enrolling and testing participants now that we have final approval from the HSRRB. If you have comments or questions regarding this Annual Progress Report, please contact me via mail (Glenn T. Stebbins, Ph.D., Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, 1725 W. Harrison, Suite 309, Chicago, IL 60612), telephone ((312) 563-3854), or electronic mail (gstebbin@rush.edu).

Respectfully submitted,



Glenn T. Stebbins, Ph.D.
Associate Professor of Neurological Sciences
Rush-Presbyterian-St. Luke's Medical Center